REVISED MI DEFINITIONS
IMPLICATIONS FOR CLINICAL TRIALS

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Rotterdam - The Netherlands
TRITON  Prasugrel  ACS + PCI

n = 13,608 moderate / high risk ACS, all PCI

CV death  MI  Death  Stroke  major bleed non-CABG

Clop  Pras  

9.1  9.7  7.4  3.2  3.0  1.0  1.0  1.8  2.4

Wiviott  NEJM 2007
TRITON Prasugrel ACS + PCI

Universal MI Classification

- CLOPIDOGREL
- PRASUGREL

29%↓

P = 0.0015

18%↓

ns

24%↓

< 0.0001

Spont.

Second.

SCD

PCI

CABG

3.4

2.5

0.4

0.3

0.1

0

6.4

4.8

0

0.1
MI IN TRIALS: CEC - INVESTIGATOR

P < 0.001

9.7

7.4

3.3

Clop  Pras

TRITON

TRITON investigator

Serebruany    Thromb Haemost 2012
MI IN TRIALS: CEC - INVESTIGATOR

Serebruany    Thromb Haemost 2012

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clop</th>
<th>Pras</th>
<th>Clop</th>
<th>Tica</th>
<th>PLATO investigator</th>
<th>PLATO investigator</th>
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<tr>
<td>PLATO</td>
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<td>5.9</td>
<td>5.4</td>
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P < 0.001    ns    P < 0.001    ns
## MI IN TRIALS: CEC - INVESTIGATOR

<table>
<thead>
<tr>
<th></th>
<th>Plac</th>
<th>Abx</th>
<th>Epti</th>
<th>P</th>
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<tbody>
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<td>EPIC investigator</td>
<td>12.8</td>
<td>8.3</td>
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<td>0.009</td>
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<tr>
<td>ns</td>
<td>12.4</td>
<td>9.0</td>
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<td>P = 0.04</td>
<td>15.7</td>
<td>14.2</td>
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<td>0.04</td>
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<td>P &lt; 0.001</td>
<td>10.0</td>
<td>8.0</td>
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</table>

*Plac* and *Abx* indicate placebo and active treatment, respectively. *Epti* indicates the investigator's name.
Outcome of trial may vary, depending on definitions of primary endpoints, particularly MI.

The definition should be pre-specified, according to ESC, ACC, AHA, WHF guidelines.

Similarly pre-specify definitions of bleeding, stroke etc.

Both CEC and investigator reported endpoints should be reviewed by regulatory agencies: EMA, FDA.
UNIVERSAL DEFINITION OF MI

ESC, ACC, AHA   Eur Heart J 2000
- MI = necrosis caused by ischaemia

ESC, ACC, AHA, WHF   Eur Heart J 2007
- distinguish different causes (types) of MI

ESC, ACC, AHA, WHF   EUR Heart J 2012
- more sensitive markers of myocardial necrosis
- myocardial necrosis in critically ill (MI or injury)
- myocardial necrosis with PCI or CABG
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UNIVERSAL DEFINITION OF MI

Evidence of myocardial necrosis
- Rise and/or fall of markers of necrosis (troponin) with at least one value > 99%

In clinical setting of myocardial ischaemia
- Symptoms
- New (presumed new) ST-T changes or LBBB
- Development of (new) Q waves
- Imaging evidence of loss of viable myocardium or new wall motion abnormality
- Intracoronary thrombus by angio / autopsy
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MYOCARDIAL NECROSIS

Primary myocardial ischaemia (MI type 1)

- Plaque rupture / fissure
- Intracoronary thrombus

Ischaemia by supply / demand imbalance

- Tachy-brady-arrhythmia
- Aortic dissection, severe Aortic valve disease
- Hypertrophic cardiomyopathy
- Cardiogenic, hypovolemic, septic shock
- Severe anaemia
- Hypertension (+/- LVH)
- Coronary spasm, embolism, vasculitis
- Endothelial dysfunction without significant CAD
MYOCARDIAL NECROSIS

Injury not related to myocardial ischaemia
- Cardiac contusion, surgery, ablation, pacing, defibrillator shock
- Rhabdomyolysis (cardiac involvement)
- Myocarditis
- Cardiotoxic agents (antracyclines, herceptin)

Multifactorial / undetermined myocardial injury
- Heart failure, Stress (Takotsubo) cardiomyopathy
- Pulmonary embolism, pulmonary hypertension
- Sepsis and critical ill patients
- Renal failure, stroke, intracranial bleeding
- Amyloidosis, sarcoidosis, strenuous exercise
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- more sensitive markers of myocardial necrosis
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- myocardial necrosis with PCI or CABG
Continuing discussion about relevance of PCI related myocardial injury:
- It is often unavoidable, however it is better if such injury could be limited
- It can be limited by careful catheter / wire handling and by anti-thrombotic therapy
- Even in patients with successful, elective PCI and a normal troponin level before the procedure, troponin elevation (myocardial injury) is frequent
- The long-term consequences are uncertain

Similarly, in cardiac surgery some injury is often unavoidable
44 % > 97.5\textsuperscript{th} percentile
23 % > 3 \times 99\textsuperscript{th} percentile

Troponin elevation no impact on prognosis (1 yr death / MI)

3200 patients, successful elective PCI
De Labriolle Am J Card 2009
Mortality at 6 months follow-up (%)
Akkerhuis, Simoons  Circulation 2002

PCI related

CAPTURE, EPIC, EPILOG
IMPACT II, PURSUIT
N = 8836

Spontaneous

PURSUIT
N = 5583

CK-MB elevation relative to ULN
SPONTANEOUS / PCI RELATED MI

Adjusted Risk of CV Death by MI Classification

Type 1 - Spontaneous
Type 2 – Secondary “demand”
Type 4a – PCI Related
Type 4b – Stent Thrombosis
Type 5 – CABG Related
Any Myocardial Infarction

13,602 patients, 1118 new or recurrent MI after enrollment, 6 m follow-up
TRITON-TIMI 38
Bonaca et al Circulation 2012
### SPONTANEOUS / PCI RELATED MI

5467 patients, 212 PCI related MI, 236 spontaneous MI after enrollment, 5 year follow-up. FRISC II, ICTUS, RITA-3 Damman et al Circulation 2012

<table>
<thead>
<tr>
<th>MI</th>
<th>Study</th>
<th>Hazard ratio for CV death (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>FRISC II</td>
<td></td>
<td>4.37 (2.87 - 6.67)</td>
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<tr>
<td></td>
<td>ICTUS</td>
<td></td>
<td>4.29 (2.13 - 8.64)</td>
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<tr>
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<td>RITA-3</td>
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<td>5.66 (3.42 - 9.38)</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>4.52 (3.37 - 6.06)</td>
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<tr>
<td>Procedure-related</td>
<td>FRISC II</td>
<td></td>
<td>0.99 (0.44 - 2.23)</td>
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<tr>
<td></td>
<td>ICTUS</td>
<td></td>
<td>0.38 (0.12 - 1.22)</td>
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<tr>
<td></td>
<td>RITA-3</td>
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<td>1.21 (0.30 - 4.87)</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>0.66 (0.36 - 1.20)</td>
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</tbody>
</table>
Discussion about relevance of PCI related injury:
- Elective PCI / ACS; varying follow-up
- Inclusion or exclusion of patients with elevated markers of necrosis before PCI
- Even if CK or CK-MB was normal before PCI, troponin might have been elevated
- Results may depend on method of analysis, some studies were underpowered

Consequences of PCI related myocardial injury are less severe than spontaneous MI, which is important for interpretation of trial results and for information to patients.

Damman, Wallentin, Fox, Circ 2012
In patients with normal baseline (< 99th %) troponin elevation > 5 x 99th % within 48 hours after the procedure (arbitrary) are indicative of MI, if
- Evidence of prolonged ischemia (pain > 20 min)
- Ischemic ST changes (>20 min) or new Q waves
- Angiographic evidence of flow limiting complications: side branch occlusion, no-reflow, persistent low flow, embolization
- Imaging evidence of new loss of viable myocardium or new wall motion abnormality

ESC, ACC, AHA, WHF 2012
In patients with normal baseline (< 99th %) troponin elevation > 10 x 99th % within 48 hours after the procedure (arbitrary) are indicative of MI, if

- New Q waves or LBBB
- Angiographic evidence of graft- or coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new wall motion abnormality

ESC, ACC, AHA, WHF 2012
<table>
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<tr>
<th>Troponin &gt; 99th %</th>
<th>1 - 3</th>
<th>3 - 5</th>
<th>5 - 10</th>
<th>&gt; 10</th>
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<tbody>
<tr>
<td>Spontaneous</td>
<td>1</td>
<td></td>
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<tr>
<td>Secondary</td>
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<td>CABG</td>
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REPORTING MI IN CLINICAL TRIALS

Collect blood samples at baseline and 3 – 6 hours later in patients with possible / suspected MI (ACS). Collect samples before and 3 – 6 hrs after PCI / CABG.

Assess cardiac Troponin I / T
(If Troponin cannot be measured use CK-MB mass)
Interpret using 99th percentile URL for each laboratory.

Present the definition of MI to be used in the trial analysis plan and define role of Clinical Event Cie.

Report MI, and other endpoints. (trial definitions). Also report the full data table (Guidelines) such that alternative definitions can be applied in meta-analyses.
## Reporting MI in Clinical Trials

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